UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/761,893	01/17/2001	Shih-Chieh Hung	11709-003001	6011

7590 03/04/2008

Shih-Chieh Hung
Dept. of Orthop. and Traumetology, Vet. General
201, Sec. 2, Shih-pai Road
Hospital-Taipei
Taipei, 11217
TAIWAN

EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
03/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

CONTINUATION SHEET

The amendment filed 1/15/2008 under 37 CFR 1.116 in reply to the final rejection has been ENTERED.

With respect to the rejection of claims 1, 4, 6, 9, 11, 32 and 33 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al (US Patent No. 5,811,094) in view of Riser et al (US Patent No. 6,242,247 B1) and Burkitt et al (Wheater's Functional Histology (1993), page 60), Applicant's arguments filed 1/15/2008 have been fully considered but they are not persuasive.

At section 2, the response asserts that the bone substitute plate (7) of Rieser et al has a porosity of 300 to 700 μm and a roughness of at least 20 μm (column 12, lines 44-53). The response asserts that the size of porosity is too big to serve as a filter and the size of roughness may help cells including fat cells and red cells adhere to the plate. Thus, the response asserts that Rieser et al teach a method using a bone substitute plate (7) that does not and should not function as a filter. This assertion is reiterated at sections 5 and 6, where the response also asserts that the efficiency of the method would not be as great as the method disclosed in the present specification. This is not found persuasive. Rieser et al teach that the bone substitute plate (7) contains pores that form continuous canals (open porosity) and these pores are 2 to 20 μm (e.g., column 7, line 55 to column 8, line 16). The 300 to 700 μm pores refer to the surface pores (surface roughness) (e.g., column 8, lines 1-16) and not the open porosity (disclosed as 1 to 20 μm at column 12, line 35). The size of the pores taught by Rieser et al is consistent with the size of the pores required to filter red blood cells from the sample. There is no evidence of record that indicates that the red blood cells would not pass through these pores and Applicant has not provided a side-by-side comparison of the efficacy of Rieser's culture dish and the culture dish of

the present specification to demonstrate unexpected results as they relate to the claimed invention.

Furthermore, at section 2, the response asserts that Riser et al indicate that "according to the method described in US Pat. No. 5,326,357 (Kandel), chondrocytes are applied to a layer of filter material (MILLICELL®-CM having a pore size of 0.4 μm)...For implants, this kind of inhomogenous tissue is not suitable" (column 2, lines 43~60). The complete quote is shown below:

> According to the method described in U.S. Pat. No. 5,326,357 (Kandel), chondrocytes are applied to a layer of filter material (MILLICELL®-CM having a pore size of 0.4 μm) in a mono-layer with a cell density of 1.5×10^6 cells per cm^2. In vitro culturing of the monolayer produces a thin cartilage layer in two to four weeks which, in its structure obviously corresponds to the natural articular cartilage and can be implanted as such.
>
> It is also known that cartilage can be cultivated in so called high density cell cultures. Cells are applied to a carrier and are cultured in a higher density than used for mono-layer culturing. The culture medium is added only one to two hours after bringing the cells onto the carrier. After one to three culture days, the cell layer on the carrier contracts and so-called microspheres with diameters in the range of 1 mm form. On further culturing, a cartilage-like tissue forms inside these microspheres while fibrous cartilage (perichondrium) forms on their surface. For implants, this kind of inhomogeneous tissue is not suitable.

The phrase "For implants, this kind of inhomogenous tissue is not suitable" does not describe the monolayer culture with the MILLICELL®-CM filter material, rather it describes the use of high density culture that is not a monolayer culture. Even so, the pores taught by Rieser et al are not the same size as the pores of the MILLICELL®-CM filter material. The pores of Rieser et al are 1 to 20 μm in diameter, whereas the MILLICELL®-CM filter has pores of 0.4 μm in diameter.

Moreover, at section 2, the response asserts that one of skill in the art would have found it difficult, if not impossible, to modify the method of Caplan et al to include the introduction of bone marrow aspirate into the cell space and culture dish taught by Rieser et al. This is not found persuasive, because Rieser et al teach the introduction of cells from bone marrow and teach that it is not necessary to isolate specific cell types from donor tissue before they can be brought into the cell space (e.g., column 5, lines 15-36). The combined teachings of Caplan et al and Rieser et al provide ample guidance for one to introduce cells from bone marrow aspirate into the cell space of the culture dish taught by Rieser et al.

At section 3, the response asserts that the way of culturing taught by Rieser et al is different from the present specification in that the cell space of Rieser et al has at least partly permeable walls and is introduced into a space filled with culture medium for the length of the culture period (column 4, lines 29-31). The response asserts that the present application directly cultures the MSC on the upper plate. The specification states, "Percoll fractionated or un-fractionated bone marrow cells in 10% fetal bovine serum (FBS) supplemented with Dulbecco's modified Eagle's medium containing 1 g/L of glucose (DMEM-LG; Life Technologies) and antibiotics (penicillin 100 U/ml, and streptomycin 100 μg/ml) were seeded into the culture device at a density of $10^6/cm^2$. The cultures were maintained at 37°C in 5% CO_2 in air, with medium changes first at 7 days after initial plating and then every 4 days" (page 11, lines 20-28). The cells seeded into the culture device in the present specification settle onto the top plate by gravity and are cultured. The cells on the bottom plate fall through the pores by gravity, and additional cells are removed when the medium is changed (e.g., page 14, 4-13). Riser et al teach the seeding of cells into the culture dish and the settling of cells onto the bone substitute plate by

gravity (e.g., column 7, lines 24-34). Both the prior art and present specification teach the presence of a plate with at least partly permeable wells introduced into a space filled with culture medium for the length of a culture period, where the cells settle by gravity onto the porous plate and are cultured. The response does not point to a specific portion of the specification that differentiates the present invention from the teachings of the prior art. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

At section 4, the response asserts that combining Caplan et al and Riser et al would require one to seed a cell mixture onto the Leukosorb™ filter prior to introducing the cells into the cell space of Rieser et al. This is not necessary, because the porous plate (7) of Rieser et al acts as the filter and Rieser et al teach it is not necessary to purify the cells prior to adding them to the cell space (e.g., column 5, lines 15-36). The response asserts that such a combination is trivial because the fat cells and red blood cells are filtered by the Leukosorb™ filter. This is not found persuasive, because the combined teachings of the references do not require one to use the Leukosorb™ filter. The response asserts that the combined teachings of Caplan et al and Rieser et al are different than the invention of the present specification, because the invention of the present specification allows the cells to filter down. This is not found persuasive for the reasons set forth above. The cells will settle by gravity as taught by Rieser et al. Further, the response asserts that the specification does not teach an eluting step. It is noted that the combined teachings of the references do not require an eluting step.

At sections 5 and 6, the response asserts that the hydroxyapatite column used by Caplan et al and the bone substitute pate used by Riser et al are both functioned as an anchoring

substrate which is implanted with the MSC. The response asserts that recovering MSC from the upper plate in this application was not taught in these two prior arts, and the roughness of the bone substitute plate taught by Rieser et al would increase the difficulty to recover MSC from it. The teachings of Rieser et al are not limited to hydroxyapatite. Rieser et al teach the use of any bone substitute material known in the art (e.g., column 8, lines 21-25). Rieser et al teach the production of flexible plates from collagen I, from collagen II and hydroxyapatite or from poly-lactic acid, and the construction of rigid plates from tricalcium-phosphate, from hydroxyapatite or from other inorganic bone substitute materials (e.g., column 8, lines 21-25). Caplan et al teach the removal of cells from culture dishes using a releasing agent such as trypsin with EDTA or a chelating agent such as EGTA (e.g., column 12, lines 26-41). Furthermore, there is no evidence of record that one would not be able to recover the cells from the bone substitute plate (7) of Rieser et al.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Rieser et al and Burkitt et al as applied to claims 1, 4, 6, 9, 11, 32 and 33, and further in view of Pittenger et al, Applicant's arguments filed 1/15/2008 have been fully considered but they are not persuasive for the reasons set forth above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/